## REMARKS

Claims 1-47 were under consideration in the instant application. Claims 1-27 and 41-47 have been canceled, without traverse, as being directed to a non-elected invention and claims 37, 38, 39, and 40 have also been canceled, without traverse. Claims 28, 30, 33, 35, and 36 have been amended and new claims 48-58 have been added. Accordingly, claims 28-36 and 48-58 will remain pending upon entry of this amendment. In addition, the specification has also been amended to a correct sequence listing identifier.

Support for the amendments to the claims may be found in the original claims as filed and in the specification. Support for new claims 48, 49, and 51 may be found at, for example, page 27, line 4 of Applicants' specification. Support for new claims 50 and 52 may be found at, for example, page 27, line 25 of Applicants' specification. *No new matter has been added.*

Cancellation of and/or amendment to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in another patent application.

### *Priority Information*

The Examiner has stated that "acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on July 8, 1999. It is noted, however, that applicant has not filed a certified copy of the provisional application as required by 35 U.S.C. 119(b)."

Applicants respectfully submit that Applicants intend to submit a certified copy of German Patent Application No. 19931420.9, filed July 8, 1999.

***Objection to the Specification - Possible Sequence Non-Compliance***

The Examiner has stated that "[o]n page 79 of the specification, line 22, a space has been left blank that refers to a vector pB, presumably regarding its accompanying SEQ ID NO. Please provide the appropriate sequence and SEQ ID NO for this vector if appropriate, or otherwise correct the omission appropriately."

Applicants respectfully submit that the specification has been amended to include the proper sequence identifier (SEQ ID NO:125) at page 79, line 22. SEQ ID NO:125 is included with the Sequence Listing, as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to the specification.

Furthermore, with respect to the Notice to Comply which accompanied the instant Office Action, Applicants believe that the amendment to the specification is sufficient to comply with the requirements for sequence disclosures. Applicants do not believe that a substitute paper copy or CRF of the Sequence Listing is required based on the amendment to the specification. Accordingly, Applicants respectfully request withdrawal of the Notice to Comply.

***Claim Objections***

The Examiner has objected to claims 28, 33, 35, 36, 37, 38 because of the following informalities "[c]laims 28, 33, 36-38 depend from non-elected claims. Claim 35, line 9, and claim 37, line 5, both refer to Tables in the specification."

Applicants have amended claims 28, 33, and 36-38 such that they do not depend from non-elected claims. In addition, Applicants have amended claims 35 and 37 such that they do not refer to Tables in the specification. Accordingly, Applicants respectfully request withdrawal of the foregoing objections to the claims.

***Rejection of Claims 30 and 35 Under 35 U.S.C. §112, Second Paragraph***

The Examiner has rejected claims 30 and 35 under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[c]laim 30 recites the limitation "said culture" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 35 depends from claim 27, which is a composition claim (perhaps replacing "27" with -28— in line 1 would be remedial)."

Applicants respectfully submit that claim 30 has been amended such that it does not refer to "said culture," thereby obviating the rejection.

Claim 35 was amended in the Preliminary Amendment dated December 19, 2001, so that it depends from claim 28. Therefore, Applicants respectfully submit that the dependency of claim 35 is proper. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 30 and 35 under 35 U.S.C. §112, second paragraph.

***Rejection of Claims 28-40 Under 35 U.S.C. §112, First Paragraph***

The Examiner has rejected claims 28-40 under 35 U.S.C. §112, first paragraph, as "failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner is of the opinion that

> [t]he specification and claims do not describe elements which are essential to various functions of the claimed invention, including those essential to the genera comprising *fine chemicals, metabolic pathway nucleic acid molecules, allelic variants or homologues* of SEQ ID NO: 1, or nucleic acid encoding SEQ ID NO: 2. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of these very broad genera. The disclosure does not clarify what the common attributes are encompassed by fine chemicals, metabolic pathway nucleic acid molecules, allelic variants and homologues of the nucleic acid sequences claimed. The scope of the claims includes numerous structural variants, and the genera are highly variant because a significant number of structural differences between members of a given genus is permitted. Concise structural features that could distinguish structures or compounds within a genus from others are missing from the disclosure. No common structural attributes identify the members of the genus comprising fine chemicals, metabolic pathway nucleic acid molecules, allelic variants or homologues of SEQ ID NO: 1 or nucleic acids encoding SEQ ID NO: 2. And the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in each genus such that the common attributes or characteristics concisely identifying members of each proposed genus are exemplified. And because each genus is highly variant, the description provided is insufficient.

Applicants respectfully traverse the foregoing rejection. Claims 37, 38, 39, and 40 have been canceled, thereby rendering the rejection moot as it pertains to these claims. With respect to pending claims 28-36 and 48-56, Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding method of producing fine chemicals using a nucleic acid molecule comprising the nucleotide sequence set forth as SEQ ID NO:1, variants which are at least 90% identical to SEQ ID NO:1, or fragments thereof, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application

was filed as required by section 112, first paragraph (see M.P.E.P. 2163.02). In order to meet the written description requirement of the first paragraph of 35 U.S.C. §112, it is not necessary that a patent specification describe each and every specific member of a genus recited in a claim.

A claim to a genus of chemical compounds satisfies the written description requirement when its accompanying specification either defines by sequence a representative number of its members falling within the scope of the genus or when its accompanying specification defines the structural features common to a substantial portion of the genus *(The Regents of the University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)). For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention.

The instant specification describes how variants of SEQ ID NO:1 may be identified or produced and teaches what kind of sequence variation functional and non-functional variants of a polypeptide encoded by SEQ ID NO:1 may have (see, for example, page 32, line 3 through page 33, line 25). Furthermore, claims are not directed to any and/or all polynucleotides but rather are directed only to those which encode functional metabolic pathway proteins with a high degree of identity to SEQ ID NO:1.

Example 14 of the *Revised Interim Written Description Guidelines Training Materials* provides that a claim directed to variants of a polypeptide having SEQ ID NO:3 "that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B" with an accompanying specification that discloses a single species falling within the claimed genus, satisfies the requirements of 35 U.S.C. §112, first paragraph for written description. The rationale behind the foregoing conclusion, as presented by the *Written Description Guidelines*, is that "[t]he single

species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which Applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity."

Similarly, in the present case, claims 48, 49, and 51 are directed to methods of producing a fine chemical comprising culturing a cell whose DNA has been altered by the inclusion of a nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence shown in SEQ ID NO:1, wherein the nucleotide sequence encodes a metabolic pathway protein or methods of producing a fine chemical comprising culturing a cell containing a vector comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence shown in SEQ ID NO:1, wherein the nucleotide sequence encodes a metabolic pathway protein.

Applicants have disclosed in the instant specification assays for identifying all of the at least 90% identical variants of SEQ ID NO:1 which encode polypeptides capable of functioning as a metabolic pathway protein (see, for example, page 47, line 9 through page 53, line 2 of the specification). Thus, based on the teachings in Applicants' specification, one of skill in the art would conclude that Applicants were in possession of the claimed invention at the time of filing.

With respect to claims 50 and 52, which are directed to methods of producing a fine chemical comprising culturing a cell whose DNA has been altered by the inclusion of a nucleic acid molecule comprising 25 contiguous nucleotides of SEQ ID NO:1, wherein the nucleotide sequence encodes a metabolic pathway protein or methods of producing a fine chemical comprising culturing a cell containing a vector comprising a nucleic acid molecule comprising

25 contiguous nucleotides of SEQ ID NO:1, wherein the nucleotide sequence encodes a metabolic pathway protein, Applicants have described various fragments of the polynucleotides used in the methods of the invention.

In Example 15 of the *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement* the "theoretical specification" discloses a messenger RNA sequence, SEQ ID NO:1, which encodes a human growth hormone. The "theoretical specification" claims antisense molecules that inhibit the production of human growth hormone. The Guidelines provide that

> [c]onsidering the specification's disclosure of (1) *the sequence (SEQ ID NO:1) which defines and limits the structure of any effective molecules such that one skilled in the art would be able to immediately envisage members of the genus embraced by the claim* and 2) the functional characteristics of the claimed invention as well as a routine art-recognized method of screening for antisense molecules which provide further distinguishing characteristics of the claimed invention, along with, 3) the general level of knowledge and skill in the art, one skilled in the art would conclude that applicant was in possession of the invention.....*the claimed invention is adequately described.*

Similar to Example 15 of the *Interim Guidelines*, the instant specification describes the nucleotide sequence of the nucleic acid molecules used in the methods of the invention (SEQ ID NO:1) *which define and limit the structure of any nucleotide fragments such that one skilled in the art would be able to immediately envisage members of the genus embraced by the nucleotide fragment claims.*

Moreover, as provided in Example 15 of the *Interim Guidelines*, the generation of oligonucleotide fragments is routine. For example, (as indicated in Example 15 of the *Interim Guidelines*) any specified fragment can be ordered from a commercial synthesizing service.

Based on the foregoing teachings in Applicants' specification and the knowledge

generally available in the art, one skilled in the art would conclude that Applicants were in possession of the claimed invention at the time of filing of the application. The skilled artisan would also be able to make and use the claimed polypeptide fragments using only routine experimentation.

Accordingly, based on the amendments to the claims and the comments set forth above, Applicants respectfully request reconsideration and withdrawal of the instant rejection under 35 U.S.C. §112, first paragraph.

***Rejection of Claims 28-40 Under 35 U.S.C. §112, First Paragraph***

The Examiner has rejected claims 28-40 under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification, while being enabling for altering amino acid metabolism in an isolated host cell (i.e. reduction of lysine, accumulation of homocysteine and methionine) in vitro following transformation of the cell with a nucleic acid comprising SEQ ID NO: 1, encoding SEQ ID NO: 2, does not reasonably provide enablement for a method of producing fine chemicals comprising the transformation of an appropriate host cell with SEQ ID NO: 1, encoding SEQ ID NO: 2, or any allelic variant thereof, or any nucleic acid that is 50% homologous to SEQ ID NO: 1 or 50% homologous to a nucleic acid encoding SEQ ID NO: 2."

In particular, the Examiner points to two of the Wands Factors, and states that:

> [t]he specification teaches a reduction in lysine production, and an accumulation in homocysteine and methionine in host cells that are lysine over-expressors following transformation of these cells with SEQ ID NO: 1 in vitro. The specification fails to teach a method of producing all fine chemicals comprising the transformation of host cells with SEQ ID NO: 1. The specification also fails to teach a method of altering amino acid metabolism or producing any fine chemicals comprising the transformation

> of host cells with allelic variants or 50% homologues of SEQ ID NO: 1, encoding SEQ ID NO: 2.
>
> Furthermore, the Examiner is of the opinion that:
>
> [t]he breadth of the claims is very broad. The claims are drawn to a method of producing fine chemicals comprising the stable transformation of an appropriate host cell with SEQ ID NO: 1, encoding SEQ ID NO: 2, or any allelic variant thereof, or any nucleic acid that is 50% homologous to SEQ ID NO: 1 or 50% homologous to a nucleic acid encoding SEQ ID NO: 2. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of host cell transformation of SEQ ID NO: 1 or any nucleic acid encoding SEQ ID NO: 2, its functional allelic variants and its functional homologues whereby 50% of the sequence is homologous, and further whereby any fine chemical is produced.

Applicants respectfully traverse the foregoing rejection and submit that Applicants' specification discloses ample guidance as to how one of skill in the art would make and use the claimed invention. The pending claims are directed to methods of producing a fine chemical comprising culturing a cell whose DNA has been altered by the inclusion of a nucleic acid molecule set forth in SEQ ID NO:1, functional allelic variants, and fragments thereof, or methods of producing a fine chemical comprising culturing a cell containing a vector comprising a nucleic acid molecule set forth in SEQ ID NO:1, functional allelic variants, and fragments thereof. Furthermore, the claimed invention is directed to these methods, further comprising introducing one or more additional metabolic pathway molecules.

As the Examiner is aware, it is well known that enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). Applicants respectfully submit that any experimentation that may be required to practice

the claimed methods for producing fine chemicals constitutes routine, not undue, experimentation, and therefore the specification clearly enables the pending claims.

The pending claims require that a fine chemical be produced. Accordingly, functional polypeptides encoded by the nucleic acid molecule of SEQ ID NO:1, variants, and fragments thereof, are included for use in the methods of the invention. Applicants respectfully submit that Applicants' specification describes methods for transformation of host cells and growth of transformed host cells (see, for example, page 39, line 4 through page 47, line 7 and Examples 6, 7, 8, 9, and 10), as well as various fine chemicals (see, for example, page 12, line 9 through page 19, line 32) and methods for analyzing and purifying these fine chemicals (see, for example, Examples 9 and 10 of Applicants' specification). Furthermore, nucleic acid molecules having the nucleotide sequence of SEQ ID NO:1 and as well as functional variants and fragments thereof, are described in detail in Applicants' specification at, for example, page 23, line 30 through page 39, line 2. Accordingly, one of ordinary skill in the art would easily be able to practice the claimed methods of producing fine chemicals without undue experimentation.

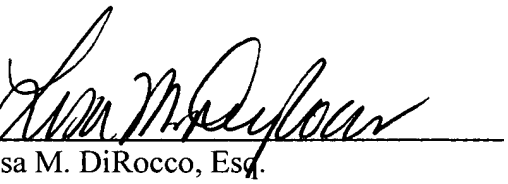
In summary, it is Applicants' position that, given the guidance in Applicants' specification and the teachings in the art at the time the invention was made, one of ordinary skill in the art would be able to practice the invention as claimed using no more than routine experimentation. Accordingly, Applicants respectfully requests reconsideration and withdrawal of the foregoing rejection.

## CONCLUSION

In view of the amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

By: 

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